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INTELLECTUAL PROPERTY **INDIA**

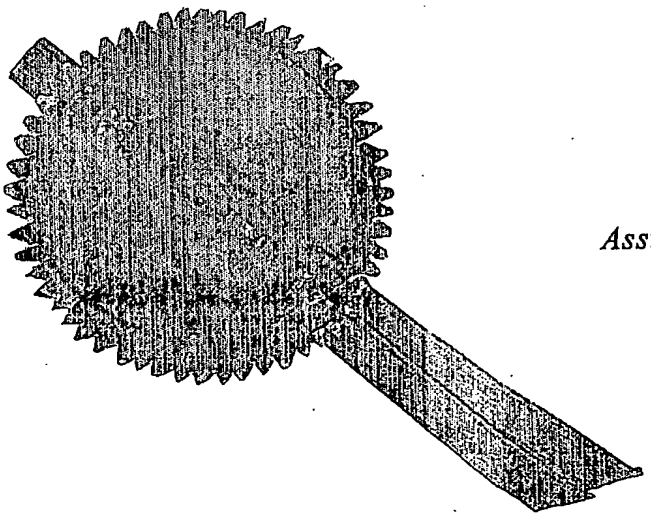
GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

REC'D 03 JUN 2005
WIPO PCT

IB/05/512

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Provisional Specification*** *filed in connection with Application for Patent No.* ***1395/Del/2004*** *dated* ***28th July 2004.***

Witness my hand this 2nd day of May 2005.



(S.K. PANGASA)
Assistant Controller of Patents & Designs

DEL 04

FORM 1

THE PATENTS ACT, 1970

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"PROCESS FOR PREPARATION OF ZIPRASIDONE HYDROCHLORIDE"**

(b) that the Provisional Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. SEEMA AHUJA
b. MAHAVIR SINGH KHANNA
c. MOHAN PRASAD
d. YATENDRA KUMAR

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE.**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
77-B, IFFCO Road, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.
Tel. Nos. (0124) 2343126, 5194271

9. Following declaration was given by the inventors or applicants in the convention country:

We, SEEMA AHUJA, MAHAVIR SINGH KHANNA, MOHAN PRASAD, YATENDRA KUMAR, of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a.

(SEEMA AHUJA)

b.

(MAHAVIR SINGH KHANNA)

c.

(MOHAN PRASAD)

d.

(YATENDRA KUMAR)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
    a. Provisional Specification (3 copies)
    b. Drawings (3 copies)
    c. Priority document(s)
    d. Statement and Undertaking on FORM – 3
    e. Power of Authority (Not required)
    f. Fee Rs.**3,000/-** (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on HDFC Bank, New Delhi.

We request that a patent may be granted to us for the said invention.

Dated this **28TH** day of **July, 2004.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

DEL 04

FORM 2

The Patents Act, 1970
(39 of 1970)

PROVISIONAL SPECIFICATION
(See Section 10)

PROCESS FOR PREPARATION OF ZIPRASIDONE HYDROCHLORIDE

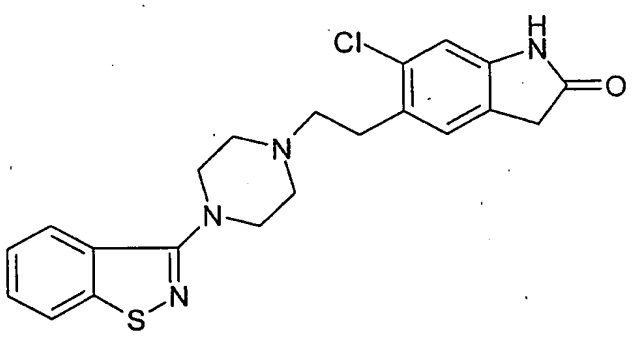
RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for preparation of ziprasidone hydrochloride.

Ziprasidone of Formula I, is chemically 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl] ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one. It is indicated for the treatment of schizophrenia. Ziprasidone is commercially available in form of its hydrochloride salt.



FORMULA I

US Patent No. 4,831,031 in Example 16 provides an analogous process for preparation of Ziprasidone hydrochloride which involves refluxing N-(1,2-benzisothiazol-3-yl)piperazine with 5-(2-chloroethyl)-6-chloro-oxindole in methyl isobutyl ketone in presence of sodium iodide and sodium carbonate for about 40 hours followed by column chromatographic purification of the product to get ziprasidone base which is dissolved in methylene chloride and treated with ethereal hydrogen chloride to get ziprasidone hydrochloride salt. The salt is washed with acetone and the product is dried.

US Patent No. 5,312,925 provides another process for preparation of ziprasidone hydrochloride which involves heating to reflux a mixture of 5-(2-chloroethyl)-6-chloro-oxindole and 1-(1,2-benzisothiazol-3-yl) piperazine in aqueous sodium carbonate for 14 hours, followed by cooling to 20°C and filtration. The wet product is re-slurried in isopropyl alcohol and filtered, washed with fresh isopropyl alcohol followed by drying under vacuum to get ziprasidone base. The base is then treated with aqueous hydrochloric acid in presence of water at a temperature of about 60-65°C for 3 to 24 hours, followed by filtration, washing with water and drying under vacuum to get ziprasidone hydrochloride.

US Patent No. 5,206,366 and 5,338,846 provide process for preparation of ziprasidone base which involves heating to reflux a mixture of 5-(2-chloroethyl)-6-chloro-oxindole and 1-(1,2-benzisothiazol-3-yl) piperazine in aqueous sodium carbonate for 13 hours followed by cooling to 25°C and filtration. The product is re-slurried in isopropyl alcohol twice and then filtered and dried under vacuum. The dried product is recrystallized from tetrahydrofuran to get ziprasidone base having a purity of 99.7% measured by HPLC.

US Patent No. 6,150,366 provides a process for preparation of ziprasidone hydrochloride from double recrystallized ziprasidone base having a purity of about 99.7% by HPLC. The process involves refluxing a slurry of ziprasidone base in tetrahydrofuran and water to get clear solution followed by addition of aqueous hydrochloric acid solution at 60-62°C in two lots, cooling the mixture to 13°C to complete crystallization of ziprasidone hydrochloride. The product is filtered and washed with fresh cold tetrahydrofuran.

The present inventors have found that following US '031 Patent, wherein water is not used for hydrochloride salt formation, hydrogen chloride used for formation of salt remains trapped in product and after washing the so obtained product with acetone there is formation of isopropylene ziprasidone and mesityl oxide impurities in the product. However, when water is used in the reaction and for washing the product, as in case of the '925 Patent, there is supposed to be no entrapment of hydrogen chloride in the product. Surprisingly though, the product obtained is darker in shade and forms lumps while drying which needs additional milling operation as ziprasidone having a smaller particle size is desirous for making compositions.

The present inventors have attributed these problems associated with prior-art to non-effective removal of trapped hydrogen chloride from the reaction product. The entrapped hydrogen chloride leads to degradation of ziprasidone or pharmaceutically acceptable salt thereof and leads to the formation of the impurities which either darken the color and leads to the formation of lumps or increase the impurity content.

The present inventors have now surprisingly found that after preparing ziprasidone hydrochloride as per the process of the '031 Patent, washing the product obtained with water, suitable organic solvent or mixture thereof for repeated time till the washings are

free of acidity to ensure complete removal of hydrogen chloride is necessary to prevent impurity formation.

Accordingly, the invention provides a process for preparation of ziprasidone hydrochloride wherein the said process comprises of

a) treating ziprasidone base with hydrogen chloride,
b) isolating the ziprasidone hydrochloride by filtration,
c) washing the product obtained with water, polar aprotic solvent, C_{1-4} straight or branched chain alkanol, C_{4-10} ether or mixtures thereof till the washings are free of acidity,
d) isolating ziprasidone hydrochloride and optionally drying the product obtained thereof.

Ziprasidone base is prepared as per our pending Indian Patent Application No. 307/DEL/2004 dated February 27, 2004. It is also possible to prepare ziprasidone base as per the processes exemplified in the '031 or the '925 Patent.

The so obtained base is treated with hydrogen chloride in presence of a suitable organic solvent. Hydrogen chloride in gaseous form, aqueous solution of hydrogen chloride or solution of hydrogen chloride in an organic solvent can be used. The solution of hydrogen chloride can be prepared in C_{4-10} straight chain or cyclic ethers, C_{1-4} alkanols, C_{2-10} esters or C_{3-11} ketones. The organic solvent used for the reaction can be selected from group comprising of water, C_{1-4} alkanols, C_{4-10} ethers, C_{3-11} ketones or mixtures thereof. The hydrochloride salt formation can be carried out at temperatures ranging from 0 to 60°C for 1 to 45 hours.

After completion of the reaction, the product obtained is isolated and the washed with water, polar aprotic solvent, C_{1-4} straight or branched chain alkanol, C_{4-10} ether or mixtures thereof till the washings are free of acidity. Such washing can be accomplished while the product is in centrifuge or in suitable filter or in a reaction vessel. Washing the product can be carried out at lower temperature using pre-cooled washing solvents as mentioned above. Polar aprotic solvent is selected from N,N-dimethylformamide, 1,4-dioxane, acetonitrile, tetrahydrofuran and N,N-dimethylacetamide. C_{1-4} straight or branched chain alkanol can be selected from

methanol, ethanol, n-propanol, isopropyl alcohol and t-butanol. C_{4-10} ether can be selected from diethyl ether, diisopropyl ether, methyl t-butyl ether and petroleum ether.

After ensuring the complete removal of trapped acidity, the product is isolated and optionally dried under vacuum at about 35 to 55°C to get ziprasidone hydrochloride.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLE 1

PREPARATION OF ZIPRASIDONE BASE

To de-ionized water (1.5 Lit) was added 5-(2-bromoethyl)-6-chloro-oxindole (75 g) and 1-(1,2-benzisothiazol-3-yl) piperazine (132 g) at 30-35°C. The mixture was slowly heated under stirring to 98-100°C over 60-80 minutes. The resultant mass was stirred for 4-5 hours at 98-100°C. After completion of reaction as monitored by HPLC, the suspended solid material was filtered at 98-100°C. The wet cake obtained was suspended in to de-ionized water (1.5 Lit) and heated to 90-95°C and further maintained for 30 minutes. The solid suspension was filtered at 90-95°C. The wet cake was further added to isopropyl alcohol (1.5 Lit) and the resultant mass was heated to reflux and maintained at reflux for 1 hour. The mass was further cooled to 30-35°C and stirred for 2 hours at 30-35°C. The solids were filtered and washed with isopropyl alcohol (75 ml) and dried under vacuum at 50-55°C for 7-8 hours till moisture content is not more than 1.0% w/w.

The product obtained was suspended in tetrahydrofuran (2.37 Lit) and heated to reflux (65-67°C. Maintained the resultant mass under reflux for 10-15 minutes. Added de-ionized water (190 ml) at 65-67°C and further stirred under reflux at 65-67°C for 15-20 minutes to get clear solution. Added activated carbon (9.5 g) to the clear solution at 65-67°C with stirring for 1 hour at 65-67°C. Filtered the reaction mass while hot under

vacuum through celite bed at 65-67°C. Washed the celite bed with tetrahydrofuran (190 ml). Recovered the solvent under vacuum at 50-55°C leaving behind about 78 ml of the reaction mass. The resultant suspension was cooled under stirring slowly to 35°C and maintained for further 30 minutes. Further cooled to 3-5°C and maintained for 2 hours under stirring at 3-5°C. The solid separated were filtered and the wet cake was slurry washed with isopropyl alcohol (285 ml). The product was then dried under vacuum at 50-55°C for 7-8 hours till the moisture is less than 0.5 % w/w.

Yield: 67 g (71%)
Purity: greater than 99.75% by HPLC
Impurity: Total impurities not more than 0.25% by HPLC

EXAMPLE 2

PREPARATION OF ZIPRASIDONE HYDROCHLORIDE

To substantially pure ziprasidone base (100 g) was added dichloromethane (2.0 Lit) and stirred for 15-20 minutes at 30-35°C. To the mixture added ethereal solution of hydrogen chloride (95.7 ml) over a period of 5-10 min at 30-35°C under stirring. The suspension was further stirred for 17-20 hours at 32-35°C and separated solids were filtered under vacuum and nitrogen atmosphere at 32-35°C. Wet solid were washed with diethyl ether (100 ml). The wet cake was suspended in water (500 ml) at 20-25°C and stirred for 30 minutes at 20-25°C. The mass was filtered and re-suspended in water (500 ml) and after stirring for approximately 1 hour, filtered and the cake was washed with a pre-cooled mixture of water and isopropanol (2 x 250 ml, 1:0.25). The washings were found to be free of acidity (pH of about 7). The product obtained was dried under vacuum at 55-60°C for 12-15 hours till the moisture content was less than 0.5 % w/w.

Yield: 105 g (94%)
Moisture content by Karl Fischer: Less than 0.5 % w/w
Purity: greater than 99.9 % by HPLC.
Impurity: Total impurities not more than 0.1% by HPLC

Dated this **28TH day of July, 2004.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

DEL 04

ABSTRACT

PROCESS FOR PREPARATION OF ZIPRASIDONE HYDROCHLORIDE

The present invention relates to a process for preparation of ziprasidone hydrochloride.

PCT/IB2005/000512